TYROSINE KINASE INHIBITORS AND ASTHMA

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The pathogenesis of allergic asthma involves the interplay of inflammatory cells such as T cells, B cells, eosinophils, mast cells and macrophages, and resident cells such as airway smooth muscle cells, epithelial cells and fibroblasts, and of their secreted mediators including cytokines, chemokines, growth factors and inflammatory mediators. Cumulative evidence concurs to the fact that tyrosine kinases play a pivotal role in initiating immune responses of inflammatory cells and airway resident cells. Tyrosine kinase can be divided into receptor tyrosine kinases and non-receptor tyrosine kinases. Receptor tyrosine kinases have been shown to be important in the pathogenesis of airway remodeling. Activation of epidermal growth factor receptor (EGFR) kinase and platelet-derived growth factor receptor (PDGFR) kinase leads to hyperplasia of airway smooth muscle cells, epithelial cells and goblet cells. Stimulation of non-receptor tyrosine kinases (e.g. Lyn, Src, Lck, Syk, ZAP-70, Fyn, Btk, Itk) is the earliest detectable signaling response upon antigen-induced immunoreceptor activation in mast cells, T cells, B cells, eosinophils and macrophages. Immune receptor includes the high-affinity IgE receptor (FcεRI), high-affinity IgG receptor (FcγRI), T cell receptor (TCR) and B cell receptor (TCR), and contains immunoreceptor tyrosine-based activation motifs (ITAM) essential for downstream signal propagation and eventual biological responses such as degranulation, and cytokine and chemokine production. Cytokine receptor dimerization upon ligand stimulation specifically induces activation of Janus tyrosine kinases (JAK1, JAK2, JAK3 and TYK2), leading to recruitment and phosphorylation of signal transducer and activator of transcription (STAT1-6) for selective gene expression regulation. Chemokine receptors (CCR1-9, CXCR1-5, CR1 and CX3CR1) are seven-transmembrane G protein-coupled receptors. Activation of chemokine receptors can trigger JAK-STAT pathway, Src family kinases such as Lck, Fyn, Lyn and Fgr, and Syk/Zap-70 to induce chemotaxis of inflammatory cells. Inhibitors of tyrosine kinases have been shown in vitro to block EGF, PDGF and transforming growth factor-α (TGF-α)-induced hyperplasia of airway smooth muscle cells, epithelial cells and goblet cells; antigen-induced inflammatory cell activation, degranulation, proliferation and cytokine synthesis; cytokine-mediated pro-inflammatory gene expression in inflammatory and airway cells; and chemokine-induced chemotaxis of inflammatory cells. More recently, anti-inflammatory effects of tyrosine kinase inhibitors (e.g. genistein, tyrphostin 47, piceatannol, AG-490, WHI-P97, Syk-antisense) in animal models of allergic asthma have been reported. Therefore, development of inhibitors of tyrosine kinases can be a very attractive strategy for the treatment of asthma.